Clinical, virological and immunological features of primary HIV-1 infection

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Introduction

Primary infection with human immunodeficiency virus (HIV) has been defined by the Centers for Disease Control (CDC) as a mononucleosis-like illness, with or without aseptic meningitis, associated with seroconversion for HIV antibody.[1]

Since the introduction of this definition in 1986, it has become clear that symptomatic primary human immunodeficiency virus type 1 (HIV-1) infection can be a recognisable clinical syndrome with distinct differences from Epstein-Barr virus (EBV) infectious mononucleosis. Moreover, the CDC definition does not encompass the full clinical spectrum of primary HIV-1 infection.

We will outline the syndrome of primary infection with HIV-1 by reviewing clinical, virological and immunological features. Differential diagnostic considerations will also be discussed.

Clinical findings

Primary infection with HIV-1 is symptomatic in the majority of cases. An acute clinical illness during the period of seroconversion has been reported with an incidence ranging from 53 to 93% of patients.[2-6] The time from infection with HIV-1 to the onset of clinical illness seems to vary between 1 and 4 weeks for the mononucleosis-like illness, and up to 6 weeks for neurological symptoms.[3 7-14] The duration of the illness ranges from a few days to 2 months, depending on the severity of symptoms.[3 5 9 15] A duration of more than 14 days seems to predispose to an early progression of HIV-1 infection to AIDS.[4]

Symptomatic primary infection with HIV-1 is most commonly described as an influenza- or mononucleosis-like illness of varying severity. Although a

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large variety of symptoms and signs have been described in association with this illness, the most frequently reported clinical features are fever, malaise, diarrhoea, myalgia, arthralgia, sore throat, headaches, lymphadenopathy and a maculopapular rash. However, there is no unanimity on the frequency of occurrence of the various symptoms (table 1).[3-5 8-39]

The acute illness is almost always febrile with temperatures ranging from 38° to 40°C, sometimes accompanied by chills. Nightsweats have also been reported in a number of patients.[3 17 19 20 40]

The most common oropharyngeal symptom is a sore throat, which in more severe cases may lead to odynophagia.[3-5 8 9 15-17 21-33 40] On examination varying degrees of pharyngeal oedema and hyperaemia without tonsillar enlargement or plaques are usually seen. Enanthem with oral ulceration appears to be a distinctive sign of primary infection with HIV-1. Ulcers have been described on the buccal mucosa, gingiva, palate and in the oesophagus.[3 9 15 17 20 26 28 30 31 33 34 40] The ulcers are usually round or oval and sharply demarcated with normal appearing surrounding mucosa. They may be covered by an exudative plaque. A typical example of such an ulcer is presented in fig 1. Similar ulcers have also been described on the anus and penis.[9 21 28] In a small number of patients oral, and even oesophageal candidiasis have been reported.[4 17 33 35 40] These manifestations of immune deficiency do not persist after the acute illness and reflect a transient suppression of the immune system. They should thus not be considered AIDS-indicator diagnoses.

Gastrointestinal manifestations of primary HIV-1 infection include diarrhoea, anorexia and nausea, sometimes with vomiting.[3-5 9 13-17 19 20 24 26-33 36-38] Some patients may complain of abdominal pain.[5 13 19 23 29 33 36]

As emphasised in the CDC definition, the most common neurological manifestation of primary HIV-1 infection is an aseptic meningoencephalitis. Complaints of headaches, photophobia and retro-orbital pain may reflect this involvement of the nervous system.[3 5 8 13 14 17 24 27 30-33 38-40] Incidental neurological findings attributed to primary HIV-1 infection include encephalopathy,[14] peripheral neuropathy,[27 37] myelopathy,[40] brachial neuritis,[34] facial palsy,[37 41] and Guillain-Barré syndrome.[32 42] In

Table 1 Frequency of symptoms reported in primary HIV-1 infection (%)

Symptoms and signs	Cooper[3] n = 46	Tindall[5] n = 39	Gaines[9] n = 20	v. Sydow[16] n = 21	Rabeneck[17] n = 16	Pedersen[4] n = 46	Cases* n = 48
Fever	92	77	100	100	n.r.	100	94
Rash	50	23	80	86	81	46	79
Lymphadenopathy	75	44	95	95	44	78	65
Sore throat	75	56	95	95	63	67	56
Nausea	67	31	n.r.	48	n.r.	n.r.	10
Diarrhoea	33	28	30	38	44	20	33
Myalgia	} 95	56	40	43	69	} 35	44
Arthralgia		49	n.r.	n.r.	n.r.		23
Headache	58	49	n.r.	n.r.	44	n.r.	33

n.r.: not reported
*: review of 48 reported cases of primary HIV-1 infection[8 10-15 18-39]

most cases these manifestations are self-limiting, although a neurological deficit after the illness has been reported.[34] Irritability and depression during the illness have also been reported.[5 14]

Primary HIV-1 infection is often accompanied by myalgia.[3-5 9 10 13-17 21-24 27 30-33 39] Increased levels of serum creatinine kinase in association with myalgia and muscle weakness have been reported in three cases.[5 23 33] In one case, primary HIV-1 infection was associated with rhabdomyelysis, acute renal failure and nephrosis.[22] Although less consistently reported, arthralgia also appears to be a common complaint.[3-5 8 10 13 15 28 30 31 33 39]

Pulmonary symptoms are infrequently reported. Some patients may complain of a dry cough without dyspnoea.[4 5 15 33 40] Two cases of acute pneumonitis have been reported.[24 33]

The most common findings on physical examination are fever, lymphadenopathy and a rash (table 1). Lymphadenopathy usually occurs in the second week of the illness and in most cases persists after the illness, although lymph nodes may gradually decrease in size. Axillary, occipital and cervical lymph nodes are most frequently involved, but the lymphadenopathy may be generalised. Mild splenomegaly has also been reported in a small number of patients.[11 17 20 21 31 37 40]
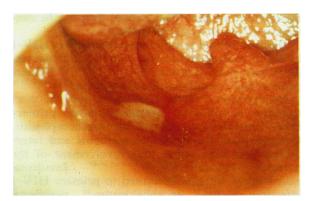

Fig 1 Oral ulceration and enanthem in a patient with primary HIV infection.

In the majority of cases a non-pruritic rash develops early during the acute illness. The rash consists of round or oval erythematous macular or maculopapular lesions with a diameter of 5–30 mm. Slight roseola-like desquamation may be present at the edges (fig 2), while the centre of the lesions can be haemorrhagic or may be covered by a crust.[43] In most cases the exanthem is symmetrically distributed over the trunk and face, but the extremities may also be affected, including the palms and soles (fig 3). The rash generally resolves within 1–3 weeks. Microscopic examination of biopsy specimens shows a lymphohistiocytic infiltrate around blood vessels and adnexae in a more or less oedematous papillary dermis. The infiltrate may contain plasma cells and there may be some extravasation of erythrocytes. The epidermis sometimes shows some exocytosis and parakeratosis.[43] However, microscopic findings are not diagnostic for HIV exanthem. Immunohistological examination shows that the infiltrate predominantly consists of CD4+ lymphocytes. Moreover, HIV p24 antigen can be detected in occasional cells, possibly Langerhans' cells, of the infiltrate. It is possible that these cells present HIV p24 antigen to CD4+ lymphocytes, leading to a delayed type hypersensitivity reaction.[20] Incidental dermatological findings include a vesiculopustular exanthem and enanthem,[34] diffuse urticaria[13] and alopecia.[13 15]

Symptomatic primary infection with human immunodeficiency virus type 2 (HIV-2), which is mainly prevalent in Western Africa, has been reported in only one case.[44] Lasting a few days, the illness consisted of fatigue, shivering, tender cervical lymphadenopathy and a maculopapular rash on the face and thorax. This case suggests that the clinical syndromes of primary infection with HIV-1 and HIV-2 are similar.

Laboratory findings
During the first 1 to 1·5 weeks after onset of the acute illness, a marked lymphopenia may develop, which can easily be missed owing to its transient

Fig 2   HIV exanthem left fore-arm with roseola-like desquamation.

nature.[5 11 18 30 31 33 45] After the initial lymphopenia the number of lymphocytes increases and lymphocytosis develops.[3 9 14 33 35 37 45] Concomitant with lymphocytosis, atypical lymphocytes may appear in the peripheral blood. T-cell subset counts during primary HIV-1 infection will be discussed later. In one study, an increase in the proportion of banded neutrophils was found during the first week of the illness and a decrease in segmented neutrophils

Fig 3   Palmar exanthem in a patient with HIV-1 infection.

during the third and fourth weeks.[9] Within two weeks after onset of symptoms, a thrombocytopenia may develop which is usually mild and asymptomatic.[3 9 13 15 30 33 35] An increase of the erythrocyte sedimentation rate has also been reported.[9] Changes in hemoglobin levels have never been described in association with primary HIV-1 infection.

Serum levels of alkaline phosphatase and aspartate transaminase may be elevated.[9 14 18 28 33 37 40] However, clinical signs of hepatitis have seldom been reported.[18]

Virological and immunological findings

During the early stages of symptomatic primary HIV-1 infection, HIV p24 antigen can be demonstrated in plasma,[15 16 26 46–50] and virus may be isolated from plasma, peripheral-blood lymphocytes and cerebrospinal fluid,[13 34 47 48 51] usually before seroconversion to HIV antibodies occurs. Following seroconversion, HIV p24 antigen generally decreases to undetectable levels and virus can less frequently be isolated.[15 16 25 31 32 48] Usually this viral clearance coincides with clinical improvement.[15 31 32 51] Persistent HIV antigenaemia seems to predispose to an early progression to AIDS.[48 52 53] In some cases a window-phase may occur in which HIV antigenaemia has disappeared prior to the appearance of HIV antibodies and thus no serological markers for HIV-1 infection can be detected.[33]

In two recent studies, the viral load during the acute illness has been quantified and related to antibody response and clinical course.[31 32] Plasma virus- and HIV p24 antigen titres during the clinical illness were high and comparable with those reported for patients with AIDS or AIDS-related complex. Decreases in viral load coincided with clinical improvement and the appearance of HIV antibodies. Levels of plasma virus- and HIV p24 antigen were undetectable 9–75 days after onset of symptoms. Transient HIV antigenaemia and virus isolation prior to seroconversion have also been demonstrated in individuals without an apparent clinical illness.[4 46 48 50 54] However, quantification of viral load has never been done in such people. It is possible that asymptomatic seroconverters have lower levels of viraemia. At any rate, the findings in all studies imply that a period exists during primary HIV-1 infection in which no HIV antibodies can be demonstrated while viraemia is present and the patient may be highly infectious.

The biological phenotype of the visus isolated during primary HIV-1 infection may have prognostic significance, that is, those people in whom a syncytium-inducing (SI) HIV variant is found appear to progress far more rapidly to AIDS than those in whom non-syncytium-inducing (NSI)

Table 2   Serological profiles during and diagnostic of primary HIV infection

At the onset of illness		Several weeks later	
p24 antigen	anti-HIV-Ab	p24 antigen	anti-HIV-Ab
+	−	−	+
−	−	−	+
+	−	+	+
−	−	+	+

viruses are isolated (Tersmette M, *et al* submitted for publication).

During symptomatic primary HIV-1 infection, HIV antibodies are usually demonstrable within the first weeks after onset of clinical symptoms. Preceding the IgG response, IgM antibodies may be detectable within 1–2 weeks after onset of the illness.[6 55–57] After 2–5 weeks peak levels are reached and then decrease to undetectable levels within 3 months. However, since an absent early IgM response has been reported in a proportion of patients, a negative result is not conclusive.[6] HIV specific IgG antibodies are usually detected 2–6 weeks after onset of the illness.[6 46–48 57 58]

Serological profiles that may be encountered in, and are diagnostic of primary HIV-1 infection are represented in table 2. In case a patient presents when already HIV-Ab seropositive (with or without concurrent HIV p24 antigenaemia), the longitudinal profile of antibodies directed against different HIV antigens may be helpful in establishing whether this is a fairly recent infection.[59]

The peripheral lymphocyte count is decreased during the early stages of the acute illness, affecting both CD4+ as well as CD8+ lymphocytes.[5 45 60] CD4+ cell counts can be as low as those seen in patients with AIDS, which may explain the occurrence of oral- and oesophageal candidiasis during primary HIV-1 infection.[61] However, the lymphopenia is transient and is followed by lymphocytosis. Although CD4+ cell counts rise as well, T-cell subset counts show that the development of lymphocytosis is mainly due to an increase of circulating CD8+ lymphocytes with progressive inversion of the CD4+/CD8+ ratio.[3 45 60 62] After approximately 4–5 weeks the level of CD8+ cells reaches a peak and returns to normal values in the following months. Since CD8+ levels remain higher than CD4+ levels, the inverted CD4+/CD8+ ratio persists.[5 45 60]

Early signs of a host response to primary HIV-1 infection include a transient appearance of interferon-alpha in the blood and raised levels of neopterin and beta$_2$-microglobulin.[60] Initially increased beta$_2$-microglobulin levels correlate with the rate of decline of CD4+ cell counts in the ensuing years.

Differential diagnosis

A diagnosis of primary HIV-1 infection should be considered in any person presenting with an acute febrile illness who belongs to a risk group for HIV infection or has a history of possible recent exposure to HIV. In a prospectively studied group of homosexual men, primary HIV infection was the second most frequent cause (after influenza) for an acute febrile illness lasting more than three days.[64] The index of suspicion for a diagnosis of primary HIV-1 infection is increased when the patient complains of a sore throat, myalgia, arthralgia, headaches, diarrhoea or neurological symptoms and physical examination shows a maculopapular rash, mucocutaneous ulceration or lymphadenopathy.

Although the clinical presentation of primary HIV-1 infection as described above is quite distinct, several differential diagnoses should be considered (table 3). Dermatological manifestations of primary HIV-1 infection are valuable diagnostic signs. Since the maculopapular rash in secondary syphilis is very similar to the HIV exanthem and the patients history often reveals high risk sexual behaviour, secondary syphilis is the most important dermatological differential diagnosis. Differentiation will be possible by serological testing for syphilis and HIV.

Lesions in pityriasis rosea greatly resemble those seen in primary HIV-1 infection. However, pityriasis rosea is mainly distributed over the trunk and upper extremities and often begins with a solitary herald patch, followed by the exanthem in 5–15 days. Moreover, constitutional symptoms are mild or absent in pityriasis rosea and there may be mild to moderate pruritus.

CMV and toxoplasma infections are usually not associated with an exanthem. In rubella the palms and soles are not affected. In patients using medication, especially antibiotics, a drug eruption should be included in differential diagnosis.

The previously described mucocutaneous ulceration in primary HIV-1 infection is an unusual finding in most other diagnoses and may aid in differentiation.

As is suggested by the CDC definition, the clinical features of EBV infectious mononucleosis and primary HIV-1 infection are similar. However, there are some distinct differences which may enable differentiation.[65] In infectious mononucleosis, the onset of the illness is insiduous rather than acute. Although a sore throat is a common complaint in both illnesses, examination of the throat in infectious mono-

Table 3   Differential diagnoses of primary HIV infection

Epstein-Barr virus infectious mononucleosis
Influenza
Cytomegalovirus infectious mononucleosis
Secondary syphilis
Pityriasis rosea
Toxoplasmosis
Rubella
Drug allergy

nucleosis usually reveals tonsillar enlargment and exsudative plaques, whereas in primary HIV-1 infection findings usually are pharyngeal oedema and hyperaemia. Moreover, in primary HIV-1 infection ulcers may be seen on the buccal mucosa, gingiva, palate or tonsils, whereas oral ulceration is a rare finding in infectious mononucleosis and, if present, is restricted to the tonsils. In contrast with primary HIV-1 infection, infectious mononucleosis is infrequently associated with a rash. Other symptomatological differences are a relatively high incidence of splenomegaly, jaundice and elevated serum levels of liver enzymes in infectious mononucleosis when compared to primary HIV-1 infection, and a relatively high incidence of diarrhoea in primary HIV-1 infection when compared with infectious mononucleosis. Lymphocytosis with increased numbers of CD8+ lymphocytes is found in both illnesses. Although the appearance of atypical lymphocytes in the peripheral blood is also a feature of both diseases, the incidence of atypical lymphocytosis appears to be considerably lower in primary HIV-1 infection than in infectious mononucleosis.

A definite diagnosis can usually be made by serological testing for both HIV and EBV. However, a false positive Paul-Bunnel test during primary HIV-1 infection has been reported.[38] A pitfall in diagnosis may thus occur, considering the previously mentioned window phase during primary HIV-1 infection, in which no serological markers for HIV can be detected.

Therapeutic options

Treatment with the antiretroviral drug zidovudine (3'-azido-3'-deoxythymidine, AZT, Retrovir®) has led to substantial clinical benefits, transient immunological improvement and suppression of viral replication in patients with late stage HIV-disease and in asymptomatic HIV infected subjects with peripheral blood CD4+ lymphocyte counts below 500/mm³.[66 67]

A few people with recently acquired HIV infection have received zidovudine. In an Australian-Swedish study, 11 subjects with symptomatic primary HIV-1 infection were treated with 1 g zidovudine daily for a median period of 56 days. Compared with a group of historical controls, there was no clear evidence of any clinical benefit in terms of resolution of the acute illness and no indication that the treatment would prevent development of persistent infection.[68] In three cases of accidental or suicidal inoculation with HIV infected blood, zidovudine-treatment instituted within 45 minutes to 6 hours after inoculation, failed to prevent the establishment of HIV infection.[69-71]

Thus, although experience with antiretroviral treatment of primary HIV infection is very limited, on the basis of the data available at present, it appears unjustified to prescribe zidovudine to persons with primary HIV infection outside the setting of a controlled trial.

Conclusion

Symptomatic primary HIV-1 infection is a more distinct clinical syndrome than appears from the CDC definition. Moreover, the clinical spectrum of primary HIV-1 infection is more extensive than has been outlined in the CDC definition. Considering the occurrence of oral and oesophageal candidiasis in association with low levels of circulating CD4+ lymphocytes and high levels of serum HIV p24 antigen, the clinical syndrome may even resemble AIDS-related complex or AIDS.

If primary infection with HIV-1 is suspected in a patient, a definite diagnosis can be made by finding a diagnostic serological profile (table 2). Considering the occurrence of a window-phase in which no serological markers for HIV-1 infection can be detected, a failure to demonstrate HIV p24 antigen does not exclude primary HIV-1 infection. Sequential testing for HIV antibodies in the serum to document seroconversion, is necessary to prevent this pitfall in diagnosis of primary HIV-1 infection.

Clinical recognition of primary infection with HIV is of importance in controlling the spread of the AIDS epidemic, since counselling efforts to limit spread of the infection can be made at an early stage of HIV infection. Early monitoring of infected persons may be of importance in optimal targetting of antiretroviral therapeutic intervention. Controlled studies are needed to assess the value of zidovudine in the treatment of primary HIV infection.

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